ALS Research Forum e-Newsletter Vol. 151 **May 13, 2016**

Visit the ALS Research Forum to read the complete stories featured in this e-newsletter. Friends and colleagues can sign up for the newsletter here. Follow us on Facebook and Twitter for the latest updates.

FDA Guidance Document - Open Comment Period Ends May 30

The ALS research community is encouraged to review and comment on the Draft FDA Guidance Document on ALS Drug Development. The deadline for submitting comments is May 30, 2016. For more information about the FDA guidance document to submit comments, click here. To download the draft guidance, click here.

Conference News

Highlights from the ALS Association's Annual Drug Company Working Group

At the annual ALS Association ALS Drug Company Working Group, ALS researchers from academia and industry convened to discuss avenues for advancing ALS research and therapy development. Held in Vancouver, British Columbia in conjunction with the American Academy of Neurology (AAN) Meeting, the meeting opened with a presentation by Ammar Al-Chalabi of King's College London about the genetics of ALS. Next, the Cytokinetics' VITALITY-ALS trial was presented by Jinsy Andrews (see July 2015 news), and Biogen's Methodology Study of Novel Outcome Measures to Assess Progression of ALS (Feb 2016 news) was presented by Elizabeth McNeil. David Ennist of Origent Data Sciences closed the scientific presentations with details about the company's computational approaches for predicting disease progression, which will be tested in the ongoing VITALITY-ALS trial in collaboration with Cytokinetics (see March 2016 news). Click here to read highlights of the meeting.

Research News

C9ORF72 Antisense Therapy Shows Promise in New Mouse Model

A new mouse model expressing hexanucleotide repeat expansions in the C9ORF72 gene points to gain-of-function as a primary mechanism of toxicity in C9ORF72 ALS/FTD, and demonstrates the feasibility of antisense oligonucleotide (ASO) therapy for C9 ALS/FTD (see Nov 2015 news). As reported in April 21 in *Neuron* online, mouse lines expressing variable C9ORF72 repeat lengths accumulated RNA foci and dipeptide repeat (DPR) proteins within several months of birth in an expression level-

dependent manner. These mice also exhibited age-dependent behavioral and cognitive impairments. Intriguingly, a single intraventricular administration of antisense oligonucleotides (ASOs) targeting the repeat RNA rapidly reduced the levels of the RNA foci and DPRs, and over a 6-month period, also alleviated anxiety-related behaviors.

New C9ORF72 Mouse Model is First to Exhibit Motor Deficits

Several mouse models of C9ORF72 repeat expansions have been developed, but despite the consistent molecular pathology, only a subset of these mice exhibit behavioral deficits or altered lifespan. A new C9ORF72 mouse model described in the Apr 21 Neuron online recapitulates the characteristic molecular features, but also exhibits neurodegeneration and behavioral phenotypes associated with ALS/FTD (see earlier report in Oct 2015 news). The mice display striking phenotypic variability, with approximately one third of mice expressing a 500-repeat variant developing an acute disease that is associated with gait abnormalities, paralysis and early death. These mice also exhibit motor neuron loss in the brain and spinal cord, as well as neuromuscular junction denervation. Other mice of the same line exhibited milder disease, while some mice appeared healthy even at one year of age. Can these mice shed light on sources of variability in the human disease?

ALS-linked ER Chaperones Disrupt Neuromuscular Function

Disruption of ER function and subsequent accumulation of misfolded proteins is a recurrent feature in ALS (see Mar 2009 news ; April 2015 news), and several ALS-linked mutations in these pathways have been identified. However, how these defects contribute to disease progression and loss of motor function is unclear. According to a new study published April 15 in the *EMBO Journal*, ALS-linked mutations in two chaperones of the protein disulfide isomerases (PDIs) family cause neuromuscular defects. Zebrafish models expressing these variants exhibited aberrant axonal morphology, disrupted synapses, and motor deficits. Deletion of one of these variants in mice led to neuromuscular junction defects, but not motor neuron loss, suggesting a role in the early stages of disease. These finding suggests that PDI dysfunction may play a role in early events in the pathogenesis of ALS, at least in subset of cases with PDI mutations.

Overactive Microglia Implicated in Progranulin-Deficient FTD

Excessive synaptic pruning by activated microglia has emerged as a common theme in several neurodegenerative diseases, including Alzheimer's and Huntington's diseases (see Nov 2015 news). According to a report in the May 5 *Cell*, excessive pruning of synapses by microglia contributes to a subset of FTD cases, and might be a driver rather than a consequence of degeneration. Mice lacking progranulin (Grn), a gene mutated in approximately 20 percent of familial FTD cases, overproduced complement proteins, and exhibited enhanced microglial infiltration and synapse elimination in brain regions associated with behavioral deficits in FTD. Crossing these mice with C1qa-deletion mice corrected many aspects of the phenotype. These findings point to the phagocytic activity of microglia as a potential therapeutic target for FTD.

SOD1 Protein Aggregates Instigate Prion-like Spreading of ALS in SOD1 Mice

Cytosolic aggregates of SOD1 protein are a hallmark of SOD1-ALS, but the role of

these aggregates in disease pathogenesis has remained unclear. According to a report in the May 3 *Journal of Clinical Investigation*, aggregates of mutant SOD1 injected into the spinal cord of mice expressing human G85R-SOD1 accelerate the onset and progression of disease in these mice. Two different strains of SOD1 aggregates induced the prion-like spreading throughout the spinal cord and brainstem, but the ALS-like symptoms and rate of disease progression differed by strain. These findings, together with similar observations reported using SOD1 mouse spinal cord homogenates (Ayers et al., 2016), suggest that SOD1 aggregates may actively contribute to disease progression and spreading in SOD1 ALS.

Deals and Partnerships

Thera and RXi Partner to Develop ALS Therapies
RXi Pharmaceuticals, a clinical-stage biotechnology company focused on RNAi therapies, has exclusively licensed its sd-rxRNA technology to Thera Neuropharma to develop novel therapies for neurodegenerative diseases. The sd-rxRNA, or 'self-delivering' RNAi compounds, are designed with properties of both single-stranded antisense molecules and double-stranded RNAi, yielding potent compounds that are spontaneously taken up by cells. Building on work conducted at RXi in collaboration with Robert Brown of University of Massachusetts Medical School, Thera will initially focus on developing compounds that target superoxide dismutase 1 (SOD1) as drug candidates for SOD1 ALS. In addition, Thera will explore combination therapies of the SOD1 sd-rxRNAs compounds with its own broad spectrum neuroprotective compounds.

Voyager Highlights SOD1 and TAU Programs at R&D Day
On April 29, 2016, startup company Voyager Therapeutics conducted an R&D day for investors and media, which includes presentations on its AAV gene therapy programs for neurodegenerative diseases, including Parkinson's disease and SOD1-ALS. The company also announced two new programs: Tau-targeting therapies for FTD and Alzheimer's disease, and Nav1-targeting therapies for chronic pain. On the SOD1-ALS front, the company is currently optimizing and testing SOD1-silencing microRNA sequences, as well as the AAV capsids for viral delivery, and is planning to submit the IND application for VY-SOD101 for SOD1-ALS in late 2017. The view the full webcast, click here (available until May 29).

BioCentury Coverage of ALS Made Public for May Awareness Month
In honor of ALS Awareness Month, the biopharma and business publication BioCentury Inc. has made their recent coverage on ALS available to readers of the ALS Research Forum, including a detailed outline of preclinical and clinical products under development for ALS. To view the full report, click here.

Funding Opportunities:

NINDS Program Project Grant (P01). Applications due May 25, 2016.

Treeway Graduate Reward Program. Applications due May 31, 2016.

ALS Canada Discovery Grants. Full application due June 3, 2016.

CIRM Partnering Opportunity for Translational Research Projects. Applications due July 15, 2016.

NEW! NINDS Clinical Trial Readiness for Rare Neurological and Neuromuscular Diseases. LOI due July 18, 2016.

Full List of Funding Opportunities >>

Upcoming Meetings:

May 2016

May 19-21, 2016: Milan, Italy: Annual ENCALS Meeting.

May 28-31, 2016: Copenhagen, Denmark: Congress of the European Academy of Neurology.

June 2016

June 5-9, 2016: Whistler, British Columbia: Keystone Symposia, Autophagy, Molecular & Physiological Mechanisms.

June 12-16, 2016: Keystone, Colorado: Keystone Symposia, Microglia in the Brain.

July 2016

NEW! July 2-6, 2016: Copenhagen, Denmark: FENS Forum of Neuroscience.

Full List of Upcoming Meetings>>

Resources:

ALS Drugs in Development Database

ALSGene

Alzforum ALS Mouse Model Database

The PRO-ACT Database

NEALS Biofluid Repository Available to Researchers

VABBB ALS CNS Tissue Request Information Site

TargetALS Core Facilities